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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,694	09/26/2005	Daniel F Hanley	58719(71699)	2172

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EXAMINER	
WEBB, WALTER E	

ART UNIT	PAPER NUMBER
1612	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,694	HANLEY ET AL.	
	Examiner	Art Unit	
	WALTER E. WEBB	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7-17,22 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-17,22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/8/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/2/2009 has been entered.

Applicants' arguments, filed 9/2/2009, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

1) Claims 1-4, 7-17, 22 and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 recites the newly amended phrase "and the t-PA or the rt-PA is administered in doses of 0.1 mg, 0.5 mg, 0.75 mg, 1 mg, or 1.5 mg doses". This phrase constitutes new matter insofar as there is no support for this list of doses in regard to t-PA. These dosage amounts are only supported for rt-PA (see specification at pg. 7, lines 2-4).

Scope of Enablement--previous

2) Claims 1-4, 7-17 and 20 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating a hematoma or blood clot, does not reasonably provide enablement for preventing a hematoma or blood clot. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This rejection also applies to newly add **claims 22 and 23**.

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the

claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill level

The invention relates to preventing or treating extravascular hematoma or blood clot by administering t-PA or rt-PA. The relative skill of those in the art is high, that of an

[1] As pointed out by the court in In re Angstadt, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not

MD or PHD. That factor is outweighed, however, by the unpredictable nature of the art. As illustrative of the state of the art, the examiner cites Naff et al., (Neurosurgery 2001). The Naff et al. reference states in their Results section at page 616 that patients receiving t-PA treatment experienced an increase in clot volume in the initial 48 hour treatment indicating the possibility failure in the resolution of clots.

2. The breadth of the claims

Since the instant specification provides no limiting definition of the term "prevention", the term will be interpreted expansively. The term "prevention" may vary widely in meaning, from "preventing" a disease from occurring to "preventing" it from progressing. Nor is the term limited by any time frame.

The claims are thus very broad insofar as they suggest that one will not experience the disease when taking the claimed agent; that should one get the disease, it will not worsen; or that following its treatment, it will not recur. While such "prevention" might theoretically be possible under strictly controlled laboratory conditions, as a practical matter it is nearly impossible to achieve in the "real world" in which patients live.

3. The amount of direction or guidance provided and the presence or absence of working examples

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"experimentation".

The specification provides no direction or guidance for practicing the claimed invention in its "full scope". No reasonably specific guidance is provided concerning useful therapeutic protocols for preventing extravascular hematoma or blood clot, other than examples of treating blood clots clinically with the claimed agents provided at pages 21-34 of the specification. The latter is corroborated by the working examples.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably used for preventing extravascular hematoma or blood clot as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the claimed invention in its "full scope" a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 102--NEW

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1) Claims 1-4 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Whitelaw et al., (Archives of Disease in Childhood 1996).

Whitelaw et al. teaches a method of treating posthaemorrhagic hydrocephalus in infants by administering recombinant tissue plasminogen (rt-PA) (see Abstract). Infants (claim 23) with haemorrhagic ventricular dilation received one to five intraventricular bolus injections of 1.0 mg or 0.5 mg rt-PA at intervals of one to seven days (see Id.; see also pg. F21, left column, 2nd paragraph and Table 1). The criteria for treatment included intraventricular haemorrhage documented by ultrasound scan (see page F20, right column under **Methods**). The reference describes Figure 1 showing reduction of intraventricular blood clot after seven days (see pg. F22, right column, fifth paragraph). The hemorrhage was intracerebral insofar as it took place in the cerebrum (claim 2). The hemorrhage was subarachnoid insofar as there was bleeding into the subarachnoid space, as evidenced by delivery of rt-PA through the ventricular system into the subarachnoid space (see pg. F21, right column, first paragraph).

2) Claims 1-4, 7, 12 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Usui et al., (Neurosurgery 1994).

Usui et al. teaches a method for treating subarachnoid hemorrhage (claims 2-4), in conjunction with external ventricular drainage (claim 7), by administering tPA to human subjects (claim 23) (see Abstract and section titled “Treatment protocol”, third paragraph). Solutions of four different concentrations of tPA, 0.042, 0.125, 0.333, and 1mg/10mL, were made and administered (see Id). The injection of tPA was repeated

every 6 hours for 5 days (claim 12) (Id.). All patients underwent CT at admission and before surgery, and repeated within 24 hours of surgery, two to three times during and shortly after thrombolytic therapy (see "Radiographic assessment", first paragraph). Patients were treated within 72 hours after SAH (see "Patients and Methods", first paragraph).

Claim Rejections - 35 USC § 103--NEW

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1) Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Whitelaw et al., (supra) as applied to claims 1-4 and 23 above.

Whitelaw et al., taught above, differs from the instant claim 7 insofar as the external ventricular drainage associated with the treatment was not taught as being necessary. Drainage was used for some of the infants (see Table 1 of Whitelaw), but it is not clear whether those infants necessarily had blood clots, since only cases 3, 15, and 16 were identified in the discussion of treating blood clots.

It would have been obvious to a person having ordinary skill in the art to have administered the thrombolytic agent of Whitelaw et al. in conjunction with external ventricular drainage, since the procedure may be necessary as an added measure to clear fluid in an effort to treat posthaemorrhagic hydrocephalus in infants as evidenced by Whitelaw et al.

2) Claims 8-11, 13-15 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Usui et al., (supra) as applied to claims 1-4, 7, 12 and 23 above.

Usui et al. differs from the instant claims insofar as it does not teach administration between 12-24 or 24-48 hours after diagnosis of the subarachnoid hemorrhage, performing CT scans at intervals of about 6-24 hours, administering rt-PA about every 4, 10 or 12 hours, or a specific dose of 0.1 mg.

Established precedent holds, even a slight overlap in range establishes a prima facie case of obviousness. In re Peterson, 65 USPQ2d 1379, 1382 (Fed. Cir. 2003). Here, a prima facie case of obviousness exists where the claimed ranges for treatment after diagnosis of subarachnoid hemorrhage, 12-24 hours and 24-48 hours, lies inside the prior art range of treatment within 72 hours, which is specific enough to reasonably

suggest the instantly claimed range for treatment of subarachnoid hemorrhage. Furthermore, Usui et al. teaches that findings have been reported that removal of clot within 48 hours of SAH prevents vasospasm (see first paragraph after Abstact). Accordingly it would have been obvious to have arrived at a time for treatment within the instantly claimed range simply by following the general teachings of Usui et al.

In regard to claim 10, it would have been obvious to perform CT scans at intervals of 6-24 hours to monitor blood clot size, since Usui et al. teaches performing CT scans at admission, before surgery, and repeated within 24 hours of surgery, two to three times during and shortly after thrombolytic therapy. The artisan would have been motivated to use CT to regularly monitor the effects of treatment, especially since tPA has no ability to differentiate a pathological clot from a hemostatic clot.

In regard to claim 13, it would have been obvious to have administered the tPA about every 8 hours, since the Usui et al. teaches administering the thrombolytic agent at 6-8 hour intervals (see Abstract).

In regard to claims 11, 14, 15 and 22, MPEP 2131.03 states that a *prima facie* case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties. Here, the administering rt-PA about every 4, 10 or 12 hours is *prima facie* obvious insofar as it is reasonably close enough to every 6-8 hours such that one skilled in the art would have expected them to have the same properties. A *prima facie* case of obviousness also exists in regard to the administration of a 0.1mg dose (claim 22), since Usui teaches administering a dose of rt-PA at 0.133mg, which is

reasonable close enough that one skilled in the art would have expected them to have the same properties.

3) Claims 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Usui et al., (supra) as applied to claims 1-4, 7, 12 and 23 above, and in further view of Mayfrank et al., (Acta Neurochir (Wien) 1993).

Usui et al. differs from the instant claims 16 and 17 insofar as it does not teach stopping treatment when the blood clot is 80% of its original size, or when the blood clot is 80% of its original size about 3 days after the first administration of the thrombolytic agent.

Mayfrank et al. teaches a method of treating blood clots in the brain by administering rtPA. (See Abstract.) The reference teaches that rtPA has been known to lyse subarachnoid blood clots. (See pg. 32, right column, 4th paragraph.) Mayfrank teaches stopping treatment until CT scans demonstrate a substantial reduction of intravetricular blood (see pg. 32, left col., 1st paragraph). Mayfrank taught that ventricular size decrease was normal in all patients after 48 hours of treatment, and that the resolution of accompanying intraventricular haematomas (clots) seemed not to be accelerated by intraventricular rtPA injection. (See pg. 34, left col., 1st paragraph.)

It would have also been obvious to stop treatment when the blood clot is 80% of its original size in the method of Usui et al., since treatment includes drainage and an 80% blood clot reduction may be small enough to be eliminated by the drainage within the first three days of treatment. If all or a substantial portion of the blood has been

removed from the ventricle, there would be no need for further treatment, as evidenced by Mayfrank et al.

Response to Arguments

A declaration under 37 CFR 1.132 was also submitted by Daniel F. Hanley. The affiant attested to experiments involving patients with spontaneous intracerebral hemorrhage. Experiment I, involved treatment of obstructive hydrocephalus by administering t-PA where patients were given dosing regimens of 3.0mg every 12 hours, 1.0mg every 12 hours, and 0.3 mg every 12 hours. Results indicated that the 0.3 mg dosage regimen appeared to offer the highest rate of clot lysis (22%/day) with the lowest complication rate, but the 1.0 mg regimen offers the best demonstrated lysis rate with an acceptable safety event rate. The 3.0 mg regimen generated a lysis rate of 23.0%/day, while the 1.0mg regimen generated a lysis rate of 27.5%/day.

Experiment II involved treatment of obstructive hydrocephalus by administering t-PA where patients were given a dosing regimen of 1 mg every 8 hours. Results indicated that 43% of subjects were modified Rankin Score 0-4 at thirty days and this group's functional state improved over the next 5 months so that 49% of subjects were mRS 0-3 at 180 days.

Overall, affiant states that the results of Experiments I and II demonstrate the safety of low dose administration protocols of tPA, with decreased symptomatic bleeding as compared to higher doses of tPA. However, these results are not surprising in view of the prior art discussed above. Usui et al. teaches a low dose therapy of tPA

at doses of 0.042, 0.125, 0.333, and 1mg/10mL. The reference taught that high dose therapies have "revealed that the efficacy of tPA has been accompanied by a relatively high incidence of an inherent complication of postoperative bleeding" (see section title "Dosage and method of tissue plasminogen activator therapy", first paragraph). The reference also noted other safety concerns when higher doses are used such as confusion and development of hydrocephalic condition (see Id. at 2nd paragraph). Thus, affiants evidence demonstrating improved safety when administering a low dose administration of tPA is not unexpected.

It should also be noted here that even if affiant's data supported unexpected results, the instant claimed invention is not commensurate in scope with these data. The scope of the instant claimed invention is much broader insofar as claim 1, recites dosage regimens of 0.5, 0.75 or 1.5 with no indicated time interval, or specific disease state to be treated.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Walter E. Webb whose telephone number is (571) 270-3287. The examiner can normally be reached on 8:00am-4:00pm Mon-Fri EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Walter E. Webb
/Walter E Webb/
Examiner, Art Unit 1612

/Frederick Krass/

Supervisory Patent Examiner, Art Unit 1612